

*Perla J. van de Mheen, MSc
Louise J. Gunning-Schepers, PhD ScM*

Both authors are with the Academic Medical Center, Institute of Social Medicine, Amsterdam, The Netherlands. Ms. van de Mheen is a Research Fellow, and Dr. Gunning-Schepers is a Professor of Social Medicine.

Differences Between Studies in Reported Relative Risks Associated with Smoking: An Overview

SYNOPSIS

REPORTED RELATIVE RISKS associated with smoking differ between studies; these differences may reflect true biological differences between populations or may be research artifacts introduced by differences in factors such as amount smoked or smoking duration. The authors reviewed the literature published before June 1992 on relative risks associated with smoking for heart disease, stroke, lung cancer, and chronic obstructive lung disease. They quantified the effect of variables such as age, amount smoked, and smoking duration on reported relative risks. The main reasons for the variation in reported relative risks were: misclassification of former smokers as never smokers, the use of mortality rate ratios rather than incidence rate ratios, a possible period effect suggesting increasing relative risks over time, and differences in the amount smoked. It is far more likely that these factors are responsible for the observed variation between studies than that the variations reflect true biological differences between populations. Using relative risks from other studies is therefore justified in calculating a population attributable risk if the studies are carefully selected and address factors such as amount smoked and period effects.

The prevalence of a risk factor and the associated relative risk are important epidemiological measures. They are needed to calculate the population attributable risk, which can be used as a simple measure to show how much mortality would be avoided if a risk factor were eliminated. The potential impact fraction is another measure that is calculated based on both the prevalence of a risk factor and the associated relative risk. This measure enables us to choose between different interventions based on their expected health effects, for example, an expected reduction in mortality.

Epidemiological models such as PREVENT are designed to enable policy makers and public health professionals to quantitatively weigh alternative primary prevention interventions.^{1,2} The PREVENT model is based on the potential impact fraction and thus needs the prevalence of a risk factor and the associated relative risk as input. This epidemiological knowledge about the relationship between a risk factor and a disease is combined with a dynamic population model. The model simulates a real aging population in which mortality risks are linked through risk factors to show, for instance, that a reduction

Address correspondence to Perla J. van de Mheen, Academic Medical Center, Institute of Social Medicine, Meibergdreef 15, 1105 AZ Amsterdam, The Netherlands; tel. +31-20-5664892; fax +31-20-6972316; e-mail <p.j.vandemheen@amc.uva.nl>.

in smoking behavior will not only lead to a reduction in ischemic heart disease mortality but also to a reduction in mortality from chronic obstructive lung diseases, lung cancer, and cerebrovascular diseases. Furthermore, a time dimension is incorporated to simulate a gradual reduction in risk after cessation of exposure.³

Such epidemiological models depend on data from previously published studies. Yet large variations in disease prevalence and relative risks are found in the literature. Part of this variation may be due to differences in the measurement of other variables, which may influence both the estimated prevalence⁴ as the observed association between a risk factor and the occurrence of a disease.⁵ A problem may arise in deciding which estimates of prevalence and relative risk are the most representative for a certain population. For example, estimates of smoking-related risks for the population of the Netherlands would ideally be based on data taken from a cohort study carried out in the Netherlands. In practice, data on the prevalence of most risk factors are available from surveys. However, relative risks are not always available for the population studied and reported relative risks in a certain population are not necessarily applicable to other populations. When population-specific estimates are not available, it is important that relative risk estimates are carefully selected to best fit the specific population. This may be difficult due to the variation between studies in reported relative risks. It is thus important to find out what explains these differences between studies.

When clinical trials give different results, a meta-analysis is usually carried out. Meta-analyses can be based on published data that show the absolute number of patients in various groups; however, many population studies report relative risks without the absolute numbers. Furthermore, population studies that use different approaches, for example, cohort studies and case-control studies, are not methodologically comparable. Nevertheless, as subgroup analyses are performed in a meta-analysis to see whether there is any heterogeneity in the treatment benefit, we should try to explain the observed variation in reported relative risks and decide whether it is justified to use a relative risk from a study carried out in another country.

The authors reviewed the published literature on smoking-related diseases to determine (a) the extent of variation between studies in reported relative risks associated with smoking for heart disease, stroke, lung cancer, and chronic

obstructive lung disease and (b) the effect that this variation has on the population attributable risk for smoking and the potential impact fraction. We analyzed possible reasons for these differences in relative risks between studies, such as differences in amount smoked or smoking duration, and estimated their influence on the reported relative risk. If the influence of such variables on the reported relative risks of disease associated with smoking is strong and they are likely to explain the observed variation between studies, then it is appropriate to apply relative risks from published studies to other populations.

Methods

We analyzed 83 reports on the risks associated with smoking for heart disease, stroke, lung cancer, and chronic obstructive lung disease. These publications were selected for inclusion using the following criteria: (a) Each study was published in the international literature written in English before June 1992. (b) Only one publication for each study was selected, unless the subsequent publication(s) considered a different subgroup or gave additional information.

In the case of multiple publications, the one with the longest follow-up (the most recent) or with the most extensive documentation was used.

Differences between studies in reported relative risks associated with smoking may represent true biological differences between populations or may be artifacts. Artifactual differences may result from variables including differences in age, differences in amount smoked or smoking duration, misclassification of former smokers as never smokers,

differences in exposure to other risk factors, and differences in time since smoking cessation.

We analyzed the reported relative risks according to these variables to see whether the differences between studies would disappear. In addition, we searched the literature for studies that have investigated the effect of one of the above-mentioned variables on reported relative risks. We compared the lowest and highest reported relative risk in the studies we reviewed and calculated to what extent each of the above-mentioned variables could be responsible for such variation.

Results

We analyzed studies carried out in several countries

Relative risks are not always available for the population studied and reported relative risks in a certain population are not necessarily applicable to other populations.

Table 1. Range of reported relative risks (RR) associated with smoking

Disease studied	Men		Women	
	Lowest RR	Highest RR	Lowest RR	Highest RR
Cardiovascular disease	1.3 ²¹	2 ²⁴	1.6 ²⁴	1.6 ²⁴
Coronary heart disease	1.2 ^{15,36}	2.9 ⁹	1.0 ¹⁹	3.0 ²⁵
Myocardial infarction	1.3 ³⁷	3.6 ³⁸	1.4 ³⁸	7.2 ²⁹
Stroke	1.1 ¹⁵	3.7 ²⁵	1.5 ²⁵	5.8 ²⁸
Lung cancer	2.5 ¹⁷	134.5 ³⁹	1.3 ^{19,32}	46.8 ³⁹
Chronic obstructive lung disease	0.5 ²²	38 ¹⁸	2.3 ²²	32 ¹⁹

SOURCES: References as cited.

including the United States, the United Kingdom, other European countries, and Japan. A detailed overview of the reported relative risks for the four diseases—heart disease, stroke, lung cancer, and chronic obstructive lung disease—is available from the authors on request. Table 1 gives the lowest and highest relative risk reported for men and women for the four diagnoses. In general, we found that the lowest estimates were reported for elderly populations and low exposure categories. Except for lung cancer, the highest relative risk estimates were found in high exposure categories and in relatively young populations. Furthermore, the lowest estimates in general were found in the earlier studies. This may indicate a true increase in relative risks over time and may be due to increased exposure in more recent birth cohorts, for example, due to higher cigarette consumption. However, Doll et al. have recently shown that the increase in relative risks over time was caused by the fact that age-specific mortality among nonsmokers had decreased substantially over time while the mortality rate among smokers had remained about constant.⁶ It is thus not the higher mortality rate among smokers that is causing the higher relative risks over time but the lower mortality rate among nonsmokers.

Table 2 shows the effect of the variation in reported relative risks of several diseases on the population attributable risk due to smoking. Given such a large variation in population attributable risks, it is difficult for public health professionals to estimate the extent of the public health problem. The same issue arises when the potential impact fraction is calculated to estimate the potential health gain as a result of a 50% reduction in smoking prevalence (see Table 3). Again,

wide variation is found, making it difficult for public health professionals to determine to what extent mortality would be reduced if the prevalence of smoking were lowered.

Lower relative risks are reported for the elderly for some diseases, such as coronary heart disease⁷ and stroke,⁸ but not for others, such as lung cancer. This may be due to a cohort effect. Floderus et al. reported that the relative risks of coronary heart disease associated with smoking were higher in the younger cohorts for both men and women.⁹ However, this does not explain why lower smoking-associated relative risks in the elderly are not reported for lung cancer. The observed decline in relative risk with increasing age may be at least partly a methodological artifact. One reason for this decline may be that mortality rate ratios are usually reported rather than incidence rate ratios. Incidence rate ratios take into account only the incident events of those individuals at risk.¹⁰ A mortality rate in the population is defined as the ratio of all deaths in a certain period of time over the total number of person-years in the population (including individuals with and without the disease). In the case of a large population with the disease, age-specific increases in incidence will be diluted and will only partly be shown in mortality increases. Since smokers have a higher prevalence, this effect is stronger in smokers than in nonsmokers. Hence, the mortality rate ratio will tend to fall below the incidence rate ratio. Given the increasing prevalence of some diseases with age—for example, heart disease—a decline in the mortality rate ratio by age may be expected even if the incidence rate ratio is constant over all ages; this would be due to the relatively greater increase of disease prevalence in smokers than in nonsmokers. Such a decline in the mortality rate

Table 2. Effect of variation in reported relative risks on population attributable risk (PAR)

Disease studied	Men		Women	
	Lowest PAR (Percent)	Highest PAR (Percent)	Lowest PAR (Percent)	Highest PAR (Percent)
Cardiovascular disease	10	27	15	15
Coronary heart disease	7	41	0	38
Myocardial infarction	10	49	11	65
Stroke	4	50	13	59
Lung cancer	36	98	8	93
Chronic obstructive lung disease	-23	93	28	90

Table 3. Effect of variation in reported relative risks on potential impact fraction (PIF), assuming a 50% reduction in smoking

Disease studied	Men		Women	
	Lowest PIF (Percent)	Highest PIF (Percent)	Lowest PIF (Percent)	Highest PIF (Percent)
Cardiovascular disease	5	14	8	8
Coronary heart disease	3	21	0	19
Myocardial infarction	5	25	5	33
Stroke	2	25	7	30
Lung cancer	18	49	4	47
Chronic obstructive lung disease	-11	47	14	45

ratio should not be interpreted as a change in the etiological relationship of smoking and heart disease with age (that is, a true interaction with aging). This would also explain why the earlier studies tend to report smaller relative risks and a smaller decline with age, that is, because of a higher case fatality in those studies and therefore smaller prevalences of heart disease. Furthermore, it would also explain why the declining relative risks with age are not found for lung cancer, that is, because of the low prevalence of lung cancer due to its high case fatality rate. The effect of these dynamics on the relative risk estimates has been quantified but is reported elsewhere and will not be discussed in this paper.¹¹ However, the Framingham study reported a declining smoking-associated incidence rate ratio for coronary heart disease with increasing age, from 3.3 in the age group 35–44 years of age to 0.8 in the age group 75–84 years of age⁷ based on biennial examinations of the cohort members.¹² So there must be other explanations for the observed decline in relative risks with increasing age, including differential mortality (susceptible people die at younger ages—more smokers than nonsmokers because of smokers' higher mortality risk).

In general, relative risks increased when smoking duration increased and when the amount smoked increased. This means, for example, that if the mean smoking duration in the Netherlands is higher than in the population in which the relative risk was estimated, the calculated health benefit for the population of the Netherlands of an intervention may be underestimated by using data from another country since the relative risks used were probably too low. It is difficult to compare the reported relative risks between studies, even if these relative risks are specified according to

amount smoked and smoking duration. Studies tend to use different exposure categories or different diagnoses; for example, one study may refer to ischemic heart disease and another to myocardial infarction. The use of different diagnoses may explain part of the difference in reported relative risks between studies. For instance, the Nurses Health Study¹³ and a study by Rosenberg et al.,¹⁴ comparing patients with similar diagnoses, found similar relative risks

of myocardial infarction by amount smoked taking into account the fact that the studies were carried out in different settings (2.3, 4.7, and 6.1 for nurses versus 2.0, 3.4, and 6.5 for hospital inpatients). For stroke, the relative risk has been found to increase with the amount smoked.⁸ The only two studies that are comparable with regard to exposure categories are the U.S. veterans¹⁵ and the Whitehall study.¹⁶ The increase with amount smoked is somewhat stronger in the Whitehall study, but this may be due in part to the fact that this population was

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somewhat younger (and higher relative risks of stroke are found at younger ages). For lung cancer, smaller relative risks by exposure category were found for a Japanese cohort¹⁷ than for a British cohort,^{18,19} possibly due to differences in smoking duration, type of tobacco smoked, or smoking behavior such as inhaling, a difference in the interaction with unmeasured variables, or a genetic difference. Mizuno et al. have shown that the lower lung cancer mortality relative to daily cigarette consumption in a Japanese cohort compared to that in the British physicians' cohort resulted from a shorter duration of cigarette smoking in the Japanese cohort.²⁰ Relative risks seem quite comparable in the U.S. veterans study¹⁵ and the nine-state study,²¹ especially in the higher exposure categories. For chronic obstruc-

tive lung disease, the studies are not very comparable, even when the relative risks by exposure categories are compared. For emphysema, the relative risks found in the U.S. veterans study¹⁵ are higher, especially in the higher exposure categories, than in a study of Canadian veterans.²² Doll and Peto found even higher relative risks;¹⁸ the reason for this finding is not clear.

In a previous paper we have shown that misclassification of former smokers as never smokers may be an important cause of differences in reported relative risks associated with smoking. The increase in the percentage of "never smokers" over time within a group of men born in the same period was shown to be attributable to misclassification because differential mortality could only explain part of the increase when the group of men had aged beyond 70 years.²³ One of the reasons for this misclassification may be a change in the social desirability of smoking over time. We estimated that about 26.7% of former smokers were misclassified as never smokers, which has a substantial impact on the estimated relative risks associated with smoking. A reported relative risk of 2.0 for cardiovascular disease for instance, which is the highest relative risk reported,²⁴ would be biased to 1.7 due to such a misclassification. The lowest reported estimate is 1.3, but this is the relative risk for light smokers.²¹ The overall relative risk in this population irrespective of the amount smoked was 1.6, which is close to the 1.7 mentioned above. For stroke, a relative risk of 1.51 as reported by Shinton and Beevers,⁸ would be biased to 1.34. The relative risks associated with smoking for lung cancer and chronic obstructive lung disease are biased much more strongly as a result of this kind of

misclassification, due to higher relative risks for former smokers for these diseases (from 11.35²⁵ to 2.88 for lung cancer and from 8.21²⁶ to 1.87 for chronic obstructive lung disease). When no distinction is made between former smokers and never smokers, the bias in the reported relative risk will probably be even stronger, since former smokers are likely to have a higher risk of death than the misclassified "never" smokers or the true never smokers.

The impact of adjusting the relative risk for exposure to other risk factors seems to be small. Rosenberg et al. showed that the relative risk of myocardial infarction in men increased from 2.9 to 3.1 when it was adjusted for other risk factors.²⁷ Colditz et al. showed that the relative risk of stroke for women in every exposure category increased only

slightly after adjustment for other risk factors.²⁸ Of course, there may be other (unmeasured) variables that bias the reported relative risk, but these must be strong risk factors before they will have a considerable effect on the relative risk. Adjustment of the relative risk of stroke for strong risk factors such as hypertension and diabetes has been shown to have only a small effect on the reported relative risk.²⁸

It is even more difficult to compare the relative risk for former smokers between studies, especially since many studies only report the relative risks for the entire group of former smokers irrespective of the time since smoking cessation. For coronary heart disease, the studies that do report relative risks for former smokers specified by time since smoking cessation can be divided into two groups. One group of studies reports that it takes about five years before the excess risk of coronary heart disease associated with smoking disappears,^{27,29} while the other group claims that it takes 10 to 15 years before the risk for former smokers is the same as that of never smokers.^{15,21,30,31} One of the reasons for this difference might be that some studies use incident events as the outcome measure, while other studies use

mortality as endpoint. In the first case, only first events are considered (either nonfatal or fatal), while in the second case only fatal events are used (either first or recurrent events). The difference between studies may thus result from the fact that persons may survive for a number of years with heart disease (prevalent cases), so it takes longer before the excess risk of death due to smoking has disappeared after smoking cessation compared to the excess risk of a first coronary heart disease event. For lung cancer, this difference is not very

important due to the high case fatality rates. All studies agree on the fact that the excess risk of lung cancer remains elevated after smoking cessation, even after a long period of time. The exact number of years it takes before this excess risk is reduced to its lowest value differs between studies. Dependent upon the amount smoked, the excess risk reported is about 2, 15 to 20 years after smoking cessation.^{15,18,25,32} For chronic obstructive lung disease, only two studies report relative risks for former smokers by time since smoking cessation.^{15,18} The highest estimate found in the literature shows that the risk of chronic obstructive lung disease for former smokers who have not smoked for more than 20 years is still almost three times the risk for never smokers.¹⁵

Important reasons for the observed variation appear to include the misclassification of former smokers as never smokers, the use of incidence versus mortality as endpoint, and differences in the reported amount smoked.

Table 4. Effect of using overall or age-specific smoking prevalences and relative risks of stroke associated with smoking, assuming a 50% reduction in smoking

	Overall	< 55	55-74	75+	Weighted average
Prevalence ⁴⁰	0.34	0.33	0.34	0.23	
RR ⁶	1.51	2.94	1.75	1.11	
PAR	0.15	0.39	0.20	0.02	0.34
PIF ^a	0.07	0.20	0.10	0.01	0.17

^aAn intervention is simulated in which smoking is reduced by 50%.

SOURCES: References as cited.

Discussion

The present overview has shown that reported relative risks vary considerably between studies and that estimates of the population attributable risk for smoking or the potential impact fraction of a smoking intervention will vary accordingly. It is thus important to explain the observed variation between studies to arrive at better estimates of relative risks. Important reasons for the observed variation appear to include the misclassification of former smokers as never smokers, the use of incidence versus mortality as endpoint, and differences in the reported amount smoked. Furthermore, Doll et al. have shown that the stronger decline of the mortality rate over time in nonsmokers is responsible for the increasing relative risks associated with smoking over time,⁶ which will also explain part of the differences in reported relative risks. It is likely that these factors together largely explain the differences in reported relative risks between studies and that the variation does not reflect true biological differences between populations. This is supported by the results from migrant studies, which show that migrants to some extent "adopt" the prevalence or mortality of the country to which they migrate.^{33,34} Their resulting rates are somewhere in between those of the home country and those of the country to which they migrate.

Part of the variation between studies in reported relative risks is due to differences between studies in the amount smoked or to misclassification of former smokers as never smokers. However, part of the variation might also be due to small numbers, leading to imprecise estimates of relative risks. Unfortunately, many studies report relative risk estimates without mentioning measures of variability or the absolute numbers in every exposure group, and thus confidence intervals cannot be calculated.

This means that we can carefully apply suitable relative risks to one population from a study carried out in another country, which can then be used in calculations of the population attributable risk or in models like PREVENT. However, some cautions are in order. For example, we should be aware of the fact that misclassification of former smokers as never smokers might have affected the relative risk estimate.

Therefore, sensitivity analyses should be carried out with regard to the relative risks that are used to assess whether the results of the model are greatly influenced by the choice of relative risks. The actual selection of a relative risk may depend upon various factors. For some analyses it may be sufficient to use relative risks for coronary heart disease, while in others it is necessary to use relative risks reported for separate disease entities, for example, myocardial infarction or angina pectoris. Furthermore, it seems wise to select a relative risk from a study carried out in a Western country, since the relative risks reported from countries such as Japan are usually lower than those for Western populations and the Japanese population may not be completely comparable to Western populations in terms of historical development of health status or genetic makeup.

Different definitions of relative risks are used in different studies. Depending on the application for which we need to select an appropriate relative risk, different "types" of relative risks may be selected. To calculate the percentage of mortality that should be attributed to smoking, mortality rate ratios might be preferred. These should be age-specific to obtain the most precise estimates of smoking attributable mortality, while both the prevalence of smoking and the relative risk of death may change with age. Using the overall prevalence of smoking and an overall relative risk³⁵ rather than age-specific estimates might lead to an underestimation of both the population attributable risk and the potential impact fraction (Table 4). That such a decline in the mortality rate ratio may not reflect a true change in the etiological relationship between smoking and the risk of getting the disease is not important for the calculation of the population attributable risk. To determine whether the smoking-disease relationship changes with age, incidence rate ratios (or, rather, incidence density ratios) should be used in order to be able to interpret the possible decline with age. If mortality rate ratios were used in this case, then a decline with age should be expected for diseases with a relatively high prevalence that increases with age and increases to a greater extent in smokers than in nonsmokers—such as heart disease. We cannot conclude from such a decline in the mortality rate ratio that the etiological relationship between smoking and heart disease changes with age.

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